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Design of a protocol for combined laser hyperthermia–photodynamic therapy in the esophagus

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ABSTRACT

Photodynamic laser therapy (PDT) for esophageal cancer has recently been studied in animal and clinical trials. In several animal experiments a synergetic effect was found by simultaneously applying PDT and hyperthermia (HT). In this paper an optical fiber system is described which can be used in the esophagus for combined PDT with a 1 W dye laser and HT with a 15-40 W Nd-YAG laser. Phantoms were developed to simulate the geometry of the esophagus using cow muscle. The spatial-temporal temperature field during HT was measured. The results were compared with calculations using a coupled Monte Carlo laser transport/finite difference heat transport model using the LATIS computer program. Measurements and calculations yield a realistic description of the temperature distribution during HT under various experimental conditions. The LATIS program allows the prediction of the effects of blood perfusion for in-vivo situations. The results show that the perfusion has considerable influence on the temperature field, which must be considered for in-vivo applications.

1. INTRODUCTION

Although several methods exist for reducing the suffering of patients with cancer of the esophagus, no curative therapy is available. In recent years photodynamic therapy (PDT) for esophageal cancer has been tested in both animal and clinical trials[1]. Another method is hyperthermia (HT)[2]. In several animal studies a synergistic effect was found simultaneously applying PDT and HT[3]. Since PDT is an optical method it is reasonable to laser light for HT in a combined system.

In this paper, an experimental optical fiber system, which can be used for simultaneous PDT and HT, is described. The typical wavelength for PDT is 630 nm, which can be obtained by a dye laser. The power required is in the 1 W region. For HT, the temperature of the tissue has to be raised from 37 ^{o}C to about 46 ^{o}C. For this purpose a laser beam of about 20 W is necessary. A Nd:YAG laser (1060 nm), with a penetration depth of several mm in the tissue was chosen.

In phantom experiments, the temperature distribution in tissue during HT was measured. The results were compared with calculations. Measurements and modeling give a realistic description of the temperature distribution during HT under various experimental conditions. The results of this paper are a first step towards the development of a HT instrument, which can be combined with PDT for clinical applications.

2. MATERIALS AND METHODS

2.1 Fiber

The fiber system was manufactured by Rare Earth Medical Inc. according to customer specifications. A 6-cm long diffuser is attached to the distal end of a quartz fiber. Dielectric mirrors reflecting 630 nm (for PDT) and1060 nm (for HT) are placed at the end of the diffuser. The intensity distribution of the 630-nm radiation is cylindrical and nearly constant over the diffuser length. At1060 nm, a slight intensity increase from proximal to distal was observed, which was neglected in the calculations. The fiber system was surrounded by a 1-mm transparent flexible tube, which conducts a cooling water flow (about 40 ml/min). The experiments were performed at a power of about 20 W.

The fiber was mounted in a balloon applicator, which could be inflated by air. Thus, it was possible to adjust the fiber in the center of the 12-mm bore in the phantom. The material of the balloon was transparent for the 630 and 1060 nm radiation.

2.2 Phantom

Special phantoms were developed for these experiments (Figure 1.) A special instrument was designed to cut a cylinder of muscle tissue with 10 - 11 cm lengths and 8-cm diameter with a central bore of 12 mm. In addition a supporting system of Plexiglas and plastic strings was build to keep the tissue in the exact shape with the dimensions given above. The fiber was introduced in the central 12-mm bore. The balloon was inflated at a pressure of 3 bar yielding a direct contact with the tissue. Outside the irradiation area, the shape of the tissue is maintained using a Plexiglas tube with an outer diameter of 12 mm and a wall of 1 mm. In the base plate of the supporting system holes were provided for the precise insertion of temperature probes. During the measurements, the phantom was immersed in a water bath with a constant temperature of 36.5 ^{o}C, excluding the 12-mm central bore and the top plane (at the proximal end of the diffuser). Before the measurement we waited until thermal equilibrium was reached between the tissue and the water.

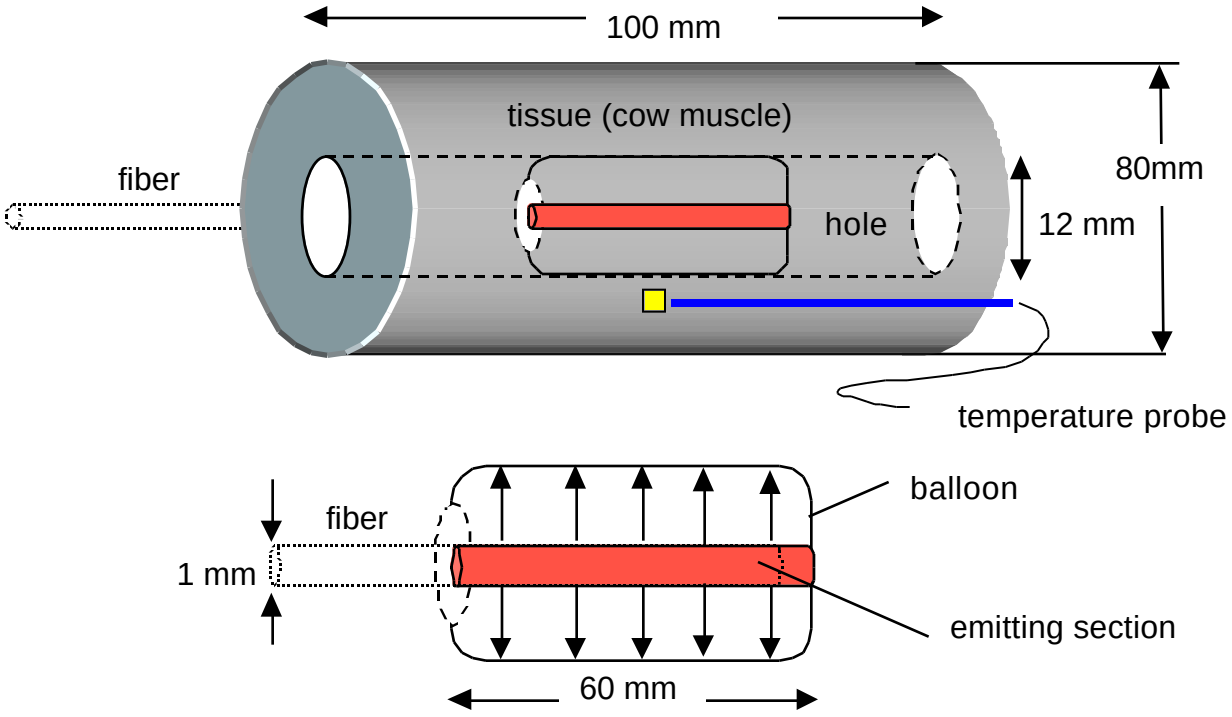


Figure 1. Schematic of tissue phantom (above) and fiber-based light delivery system (below).

3. MODEL DESCRIPTION

We have used the LATIS laser-tissue interaction computer program[4] to simulate the temperature distribution in the experiments The Monte Carlo method was used to calculate the laser light propagation in tissue. The program includes scattering in the fiber diffuser and refraction at the air tissue boundaries. Absorption of laser light goes into raising the tissue temperature according to the specific heat, approximately that of water, that is then carried away mainly by thermal heat conduction. This is modeled with the well-known bio-heat equation - a diffusion equation with cooling and heating terms due to the blood perfusion and boundary conditions. Blood perfusion was included only for the predictions for in-vivo studies, but not for the in-vitro experiments.

The thermal properties of tissue were approximated by those of water: specific heat = 4200 J/(kg K), thermal conductivity = 0.609 W/(m K) and density = 1000 kg/m^3.

The following optical parameters were used for the 1060 nm radiation: absorption coefficient μ_a = 0.36 cm^{-1} and reduced scattering coefficient $\mu'_s = \mu_s (1 - g)$ = 0.84 cm^{-1}. The optical parameters were adapted to yield agreement between measurements and calculations.

For cow muscle only one reference giving measurements for μ_a and μ'_s was found[5]. These values are three times higher than the numbers given above. Due to the difficulties to measure the optical coefficients and the biological differences in tissue samples, this discrepancy seems to be acceptable. In future experiments the optical and thermal parameters and the exact laser intensity distribution at the diffuser should be measured.

4. RESULTS AND DISCUSSION

4.1 Experiments

In Fig. 2 measurements of the temperature versus time at different depths in the phantom are shown. The tissue was irradiated for 200s at a power of 15 W. The power was switched off, when a surface temperature of 46.5 °C was reached.

For clinical application of HT the surface temperature of the esophagus should be kept at a constant value of about 46 °C for several minutes. The temperature distribution of an experiment of this type is shown in Fig. 3 for different depth in the tissue. After reaching 46 to 47 °C at the surface the laser power was lowered successively from 15 W to about 3.8 W, yielding a constant surface temperature of about 46.5 °C. After 20 min the laser power was switched off. During the irradiation nearly constant temperatures of 45, 44 and 41 °C were obtained in depth of 3, 5.5 and 12 mm.

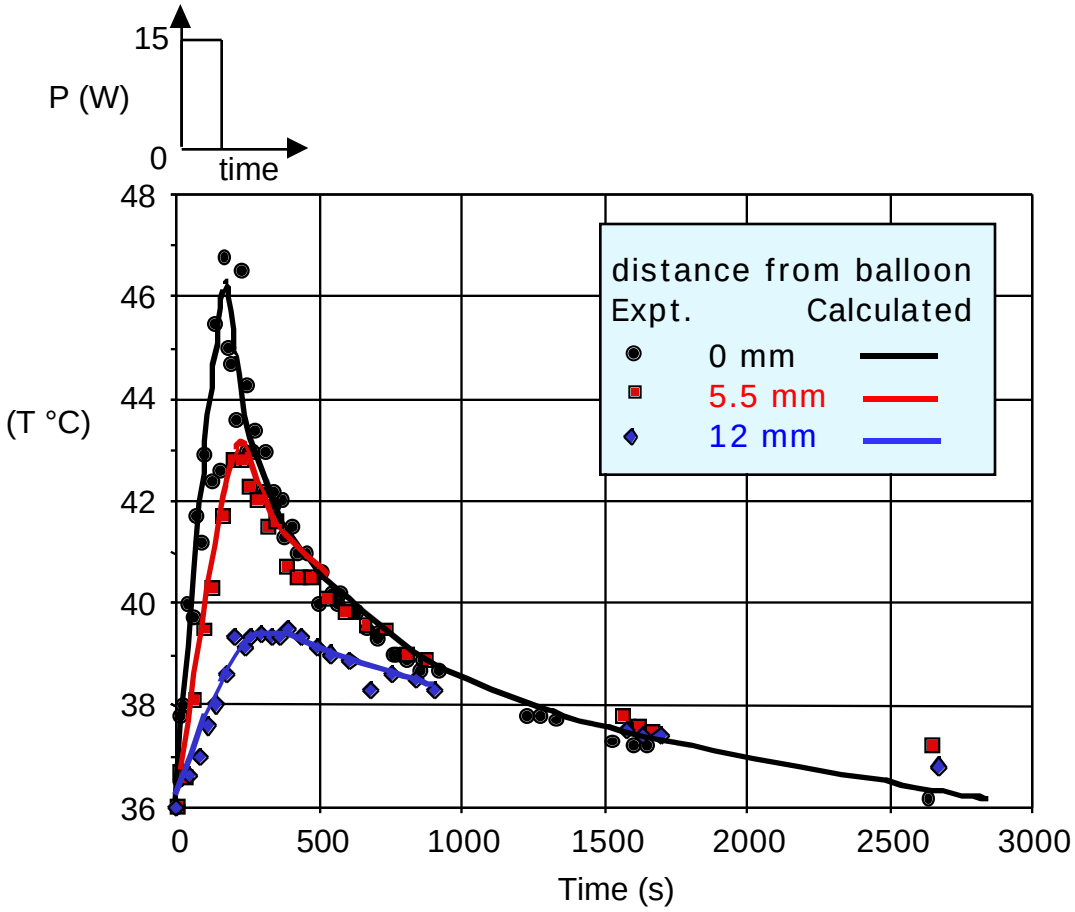


Fig. 2. Experimental data points and calculations of the temperature in the esophagus phantom during irradiation with a Nd:YAG laser (15 W. The laser was switched off at a surface temperature of 46.5 °C.

4.2 Modeling

Figure 2 shows the temperature field, which was calculated for the esophagus phantom using LATIS. The power of the Nd:YAG laser was 15 W, which was applied during 200s. The agreement between the calculations and the measurements in Fig. 2 is good.

Additional calculations were performed to reproduce the experimental results of Fig. 3 for a nearly constant surface temperature. The calculations shown in Fig. 3 are in reasonable agreement with the measurements.

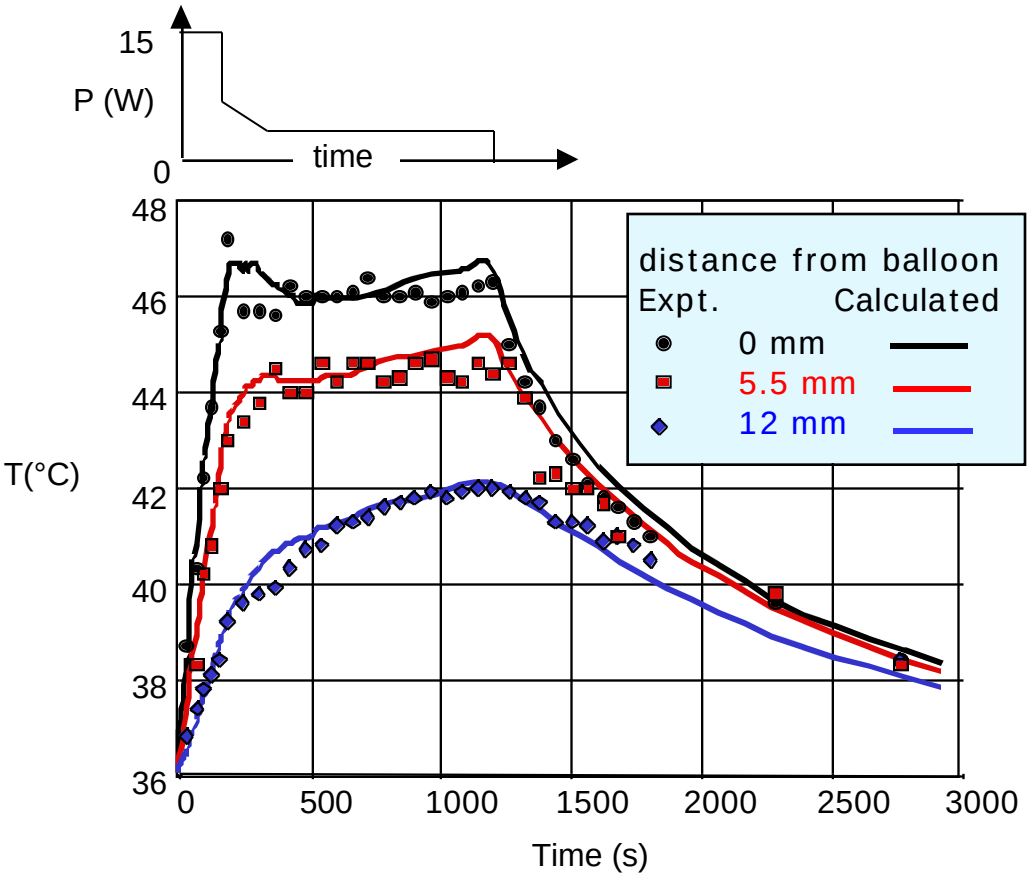


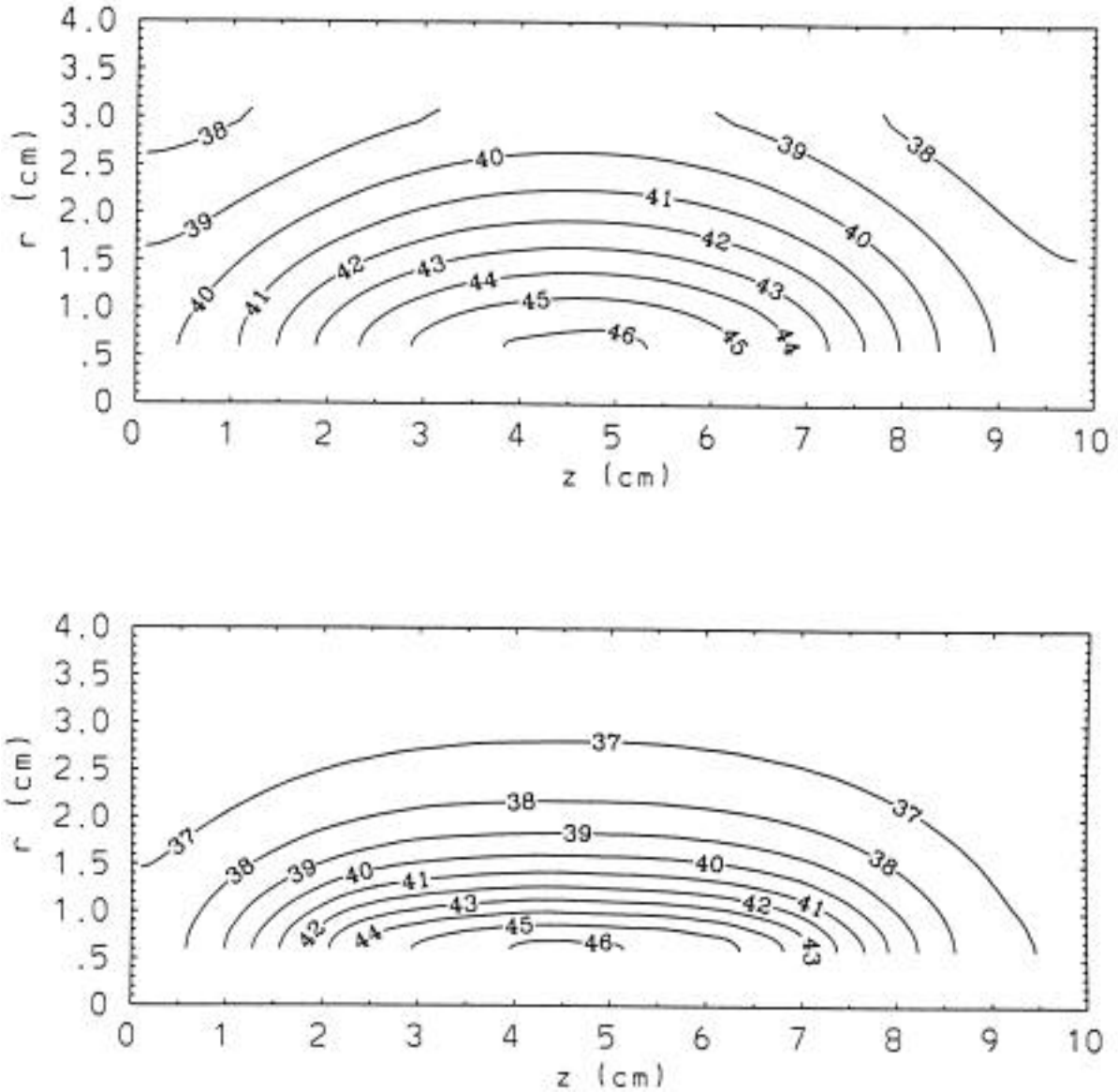
Fig. 3. Experimental data points and calculations of the temperature in the esophagus phantom during irradiation with a Nd:YAG laser (starting with 15 W). A nearly constant surface temperature of about 46.5 °C was maintained by reducing the laser power successively from 15 to 3.8 W. (15 W to 7.5 W immediately, then linear from 7.5 W to 3.8 W within 150 s, then constant 3.8 W, after 1200 s the laser was switched off). The temperature probes were at the surface (0 mm) and at depths of 3, 5.5 and 12 mm.

4.3 Design of in-vivo system, including blood perfusion

The LATIS program is able to include blood perfusion. Since perfusion data for the esophagus are not available, a typical value for tissue of 40 ml/(100g min) was used. It was assumed that this value remains constant in the temperature range from 37 °C to 46 °C. The influence of the blood perfusion on the temperature distribution was calculated. An automatic regulation of the laser power was assumed obtaining a constant surface temperature of 46 °C at the surface. Without blood perfusion a surface temperature of 46 °C is reached in 200 s using a laser power of 15 W. To maintain this temperature a mean power of only 4.2 W is necessary. With blood perfusion 25 W are required to obtain the same temperature rise in the fist 200 s. For maintaining 46 °C about 17.9 W are necessary. The blood perfusion has a strong influence on the temperature in the esophagus phantom.

The temperature fields without and with perfusion are compared in Fig. 4 a and b after maintaining a constant surface temperature of 46 °C during 1000 s (plus 200 s for heating to this temperature. The isotherms in the phantom depend on axial (z) and radial (r) coordinate. The blood perfusion has a considerable cooling effect in the tissue, reducing the effective depth for hyperthermia applications. The radial temperature gradient without blood perfusion is about 0.3 °C per mm in the center of the phantom

(Fig. 4a). Including blood perfusion this value is raised to about 0.6 °C per mm (Fig. 4b). This has a considerable influence of the effectiveness of HT in deeper tissue layers.



(Fig. 4. a) Calculated temperature distribution with no blood perfusion after 1200 s (r = radius, z = axial coordinate, the esophagus surface is at = 0.6 cm). The isotherms are shown with the temperature in °C. b) Same as Fig. a), including blood perfusion.

5. CONCLUSIONS

The paper gives experimental and theoretical information for a combination of PDT and HT for treatment of esophageal cancer. The axial and radial temperature distribution was measured in a phantom without blood perfusion during irradiation with a Nd:YAG laser for HT. A laser power of 15 W at a 6 cm long diffuser produces a surface temperature of 46 °C within 200 s. A constant surface temperature can be maintained reducing the power to about 4 W. In addition calculations were performed. The agreement between experiment and modeling is good. Modeling is important because situations can be simulated which are difficult to measure. In addition it is easy to obtain results under different conditions.

Since it is difficult to perform temperature measurements including blood perfusion the model was applied to this case. The calculations show that the blood perfusion has a considerable effect on the temperature field. To obtain the same surface temperature of 46 °C in 200s a laser power of about 25 W is necessary for the heating period. For maintaining a constant surface temperature about 18 W are required. However, the main problem is that the radial temperature gradient in tissue is approximately doubled. This means that the effective depth for HT is reduced by about a factor of two. HT is restricted more on the surface and deeper regions are excluded.

We may conclude that the combination of PDT and HT using one optical fiber is possible. Taking into account the blood perfusion the radial temperature gradient is about 0.6 °C per mm, limiting the effective depth of HT to a few mm. Another problem is the axial temperature decay. The effective length of the HT zone is about 50 % of the diffuser length.

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